relevant in the setting of slower relaxation, as may be observed in HFpEF patients. Slow incomplete relaxation can be induced by excessive afterload to such an extent that it leads to marked increases in filling pressures. When the ejection fraction is preserved, the effect of afterload is particularly evident and significantly exacerbated at higher pre-loads (2). Moreover, in contrast to normal hearts, the myocardium of heart failure patients may exhibit a flat or negative myocardial relaxation velocity to HR relationship, even at a lower range of HR (3). Consequently, lowering the HR during early exercise would prevent the clinical expression of this HR-dependent relaxation impairment.

Finally, as Reil et al. (4) recently showed, ivabradine decreases arterial elastance through an enhancement of arterial compliance and a reduction in HR. This reduction in global LV afterload could also contribute to the short-term increase in exercise tolerance described in the ivabradine-treated HFpEF patient group.

The absence of a negative lusitropic pharmacological action and the ability to modulate these diastolic function determinants (HR and afterload) make ivabradine a mechanistically very attractive drug in HFpEF treatment. Future clinical trials will give the critical verdict.

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http://dx.doi.org/10.1016/j.jacc.2013.09.064

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Reply

Effect of Ivabradine on Heart Failure With Preserved Ejection Fraction

We appreciate the interest of Drs. Santos and Leite-Moreira in our work (1). We completely agree with their comments regarding the importance of heart rate (HR) as a contributor to diastolic function. Ivabradine has a unique position as a negative chronotrope that is not a negative inotrope. Indeed, the rationale for treatment with ivabradine in our study was to avoid the reduction in the duration of diastole that follows from an increase in HR.

Disturbances in the relationship between HR and myocardial relaxation in failing hearts might represent another aspect supporting the use of If channel inhibition in this context. Although ivabradine has multiple effects, a direct effect on myocardial relaxation may be an important benefit. In addition, the potential effects of ivabradine on arterial compliance and afterload in heart failure with preserved ejection fraction (HFpEF) require, in our view, further evaluation.

The patient selection in our study was focused on patients in whom exertional dyspnea develops, which is related in part to shortening of diastole during tachycardia. The clinical effects of ivabradine are being investigated in a large multicenter study, but it is likely that this will involve a heterogeneous group. We would like to draw the attention of readers to the need for studying well-characterized subgroups of the very heterogeneous entity of heart failure with preserved ejection fraction.

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http://dx.doi.org/10.1016/j.jacc.2013.10.047

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